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Research Article

Epidemiology and Profile of Carcinoma Gall Bladder Patients

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Abstract

Introduction: Gall Bladder Cancer is third most common cancer of gastro-intestinal tract disease with variation of its prevalence geographically. According to ICMR's report about 800,000 new cases and 5,50,000 death per year reported in India. Commonest etiological factors are gall stone and chronic inflammation. Chronic cholecystitis, due to bacterial Colonization causes Carcinogenesis. Gall stone disease and gall bladder cancer reported high incidence in Gangetic belt in India. Gall bladder cancer is one of the malignancies with high mortality with < 1-year overall survival. Commonest presentation is asymptomatic presentation leads to progression of diseases in advanced stage. In India, Gall bladder cancer is more common in females and usually presented at younger age. Majority of the patients presented with Jaundice. About 10% patients presented in early stage of disease in which Radical Cholecystectomy with advanced treatment is advisable as standard treatment and can achieve about 63% of 5-year survival rate.

Material and Method: Retrospective study was conducted in the department of Radiation oncology, State Cancer Institute, IGIMS Patna. Diagnosed and histopathologically proven Gall Bladder cancers were included and details of patient data were retrieved from hospital records.

Result: In total 500 patients, common age of patients were 45 to 55 years in males and 40 to 50 years in female, 323 (64.6%) were females and 177 (35.4%) males. Commonest symptom was pain in abdomen 415 (83%), nausea and vomiting (38%), Jaundice 240 (48%).

Discussion: According to Globocon 2018, gall bladder cancer is 22nd Cancer worldwide with 219,420 new cases which is 1.2% of malignancies and about 165,087 deaths contributing 17% of cancer related death. Incidence of gall bladder cancer varies according to geographic region. High rate of incidence reported in Central and South America, Eastern Europe and South-east Asia. India has second highest number of incidences of gall bladder cancer after China.

Conclusion: Based on all available data in HBCR registry, Ca gall bladder cancer is the commonest cancer and showing increasing trend of Ca gall bladder cancer. Due to lack of awareness, poor hygiene, habit of spicy food intake, lack of exercise and fruit intake, use of unfiltered drinking water, unavailability of diagnostic facilities at rural area. Patients usually present with advance stage of disease which resulted high morality. Majority of patients subjected to Palliative treatment in the form of chemotherapy.

Keywords: Gall Bladder Cancer; Vomiting; Jaundice

Introduction

Gall Bladder Cancer is third most common cancer of gastro-intestinal tract disease with variation of its prevalence geographically [1,2]. Highest incidence of gall bladder cancer was reported in Chili, about 12.5 in 100,000 men and 27.5 in 100,000 females, reported in northern Gangetic belt, Satluj and Brahmaputra [3-5]. Other countries in South America like Bolivia and Asian Countries like South Korea, Japan and Pakistan also reported higher incidence of gall bladder cancer [3,4]. Some of the etiological factor like female sex, advanced age, gall stone disease, typhoid carriers, dietary factors, and genetic susceptibility. Progression of metaplasia to dysplasia to Carcinoma *in situ* to invasive cancer takes over the period of 5 to 15 years [6].

According to ICMR's report about 800,000 new cases and 5,50,000 death per year reported in India [7]. Commonest etiological factors are gall stone and chronic inflammation. Chronic cholecystitis, due to bacterial Colonization causes Carcinogenesis [6]. Gall stone disease and gall bladder cancer reported high incidence in Gangetic belt in India [8]. Gall bladder cancer can be present with Jaundice, hepatomegaly, ascites, duodenal obstruction or can be diagnosed after Cholecystectomy [9]. About 60% patients presented with involvement of adjacent Liver or 2nd part of duodenum. Lymph node involvement also reported in about 45% of patients in local regional area while 30% cases presented with metastasis. Five-year survival rate is quite low about 5%, due to advanced stage of disease at the time of presentation [10,11].

Gall bladder cancer is one of the malignancies with high mortality with < 1 year overall survival [12-15]. Commonest presentation is asymptomatic presentation [16] leads to progression of diseases in advanced stage. Highest incidence reported in Kamrup district 16.2 and 7.9 per 100000 woman and men [17] respectively. The risk reported seven times higher in northeastern region with incidence reported in South India. Etiological factors like obesity, older age, female gender, bacterial infection (*Salmonella typhi* and *Helicobacter billis*) gall stone specially > 3mm are shown correlation with gall bladder cancer [13,15,18,19]. Some studies shown moderate in two meals > 8hrs, exposure to various carcinogens coal/ wood duct and tobacco risk [18,20,21] can cause gall bladder cancer.

Multiple use of contraceptive pills, multiparity, early onset of menarche, late menopause has also shown association. Some of the studies shown link of prevalence of typhoid infection, arsenic exposure, geographical distribution of Gangetic belt [18,20]. In India, Gall bladder cancer is more common in females and usually presented at younger age. Majority of the patients presented with Jaundice. About 10% patients presented in early stage of disease in which Radical Cholecystectomy with advanced treatment is advisable as standard treatment [22,23] and can achieve about 63% of 5-year survival rate [24,25].

Material and Methods

Retrospective study was conducted in the department of Radiation oncology, State Cancer Institute, IGIMS Patna. Diagnosed and histopathologically proven Gall Bladder cancers were included and details of patient data were retrieved from hospital records. All details of history, physical examination, Radiological and hematological examination data were analysed. Statistical analysis done by mean, median and percentage, correlation between gall stones, stage of disease, and obstructive jaundice and tumor markers were assessed by Reasen's correlation coefficient. A total of 500 patients were analyzed from Jan 23 to Jan 24.

Results

In total 500 patients, common age of patients were 45 to 55 years in males and 40 to 50 years in female, 323 (64.6%) were females and 177 (35.4%) males. Commonest symptom was pain in abdomen 415 (83%), nausea and vomiting (38%), Jaundice 240 (48%). On examination palpable lump, was present in about 315 (63%). In personal history, tobacco chewing, and alcohol consumption were present in 104 and 87 patients. History of consuming spicy food was present in 92% patients. Patients have history of occasional fruits intake in 11% of patients. 77% presented with locally advanced disease with involvement of Liver, duodenum or pylorus, Lymph nodes and adjacent areas. 22% patients presented with metastatic carcinoma gall bladder in Liver, ovaries. 1% presented with incidental gall bladder they have been operated with cholelithiasis and after histopathological examination found as carcinoma gall bladder. On Radiological examination with ultrasound and CECT 68% presented with mass in gall bladder and 32% presented with mass and gall bladder stone.

Several tumor markers were done in all patients and values as shown below.

Patients with good performance status were planned for chemotherapy cisplatin and gemcitabine or oxaliplatin with gemcitabine. Patients who presented with jaundice were subjected to ERCP or PTBD. 240 patients presented with jaundice range from 5.12 to 40 ml/dl. After 15 or 20 days when jaundice level come down these patients were planned for chemotherapy. 13% patients were advised for Palliative care after PTBD, for pain Analgesics have been advised as per pain killer analgesics ladder pattern.

Blockage of PTBD tube is commonest problem with PTBD patients about 56%. Patients required flushing and changing of PTBD tube.

CA 19.9	88%	Above 37nm
CEA	73%	>12
LDH	38%	>240
CA 125	58%	>50
Age Group	**F (323)**	**M (177)**
<20	2	1
21-30	2	0
31-40	16	8
41-50	289	93
51-60	82	57
61-70	23	13
>70	15	5

Symptoms	**No. of Patients**
Pain in abdomen	83% (415)
Nausea and Vomiting	38% (190)
Jaundice	48% (240)
Lump in abdomen	63% (315)
Gall bladder stone	32% (160)
Tobacco chewing	20.8% (104)
Alcohol consumption	17.4% (87)
Occasional fruit intake	(55) 11%
Stage III	3%
Locally advanced disease	74%
Metastasis disease	22%
Incedental Gall bladder	1%
Adeno carcinoma	99.3%
Cholangio carcinoma	0.7%

Side effect table of Gemox and Gemcis		
No. of patients completed 4 cycles		
	Dose	No. of patients
Gem + Cisplatin	1000 mg/m^2 D1/D8 40 mg/m^2 Every 21 day	160
GEMOX + Oxaplatin	1000 mg/m^2 135 mg/m^2 Every 2 weeks	160

Table a

	Survival
Stage I	1-3 years
Stage III	10-20 months
Stage IV	4-8 months
Patients with PTBD	<6 months

Table 1: Survival durations for different patient groups.

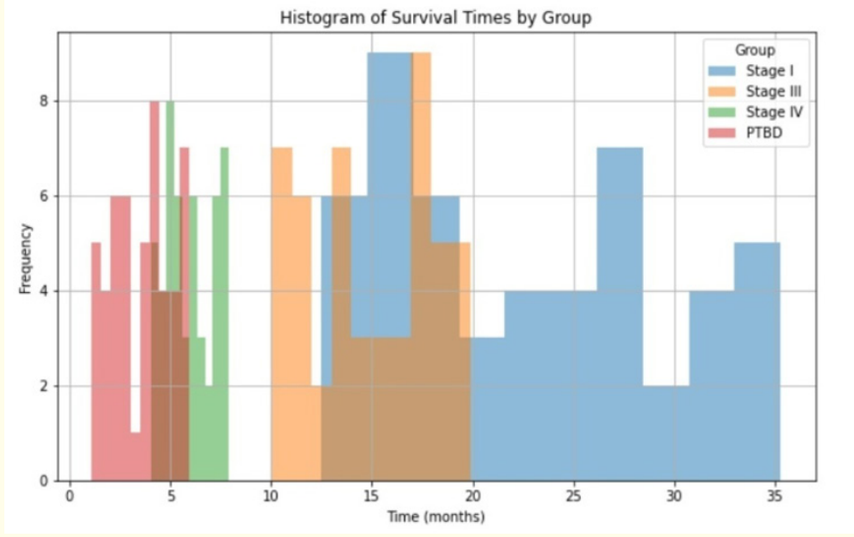

Figure 1

Gemox (%)	Gemcis (%)	Side Effect	Chi-Square	P-Value
18	42	Neutropenia	6.63	0.037
48	62	Nausea and Vomiting	3.41	0.065
53	32	Loose Motion	8.18	0.004
22	28	Anemia	0.67	0.041
78	73	Fatigue	0.43	0.051

Table 2: Gemox vs. Gemcis: Side Effect.

Category	(%)
Discomfort	88
Blockage	56
Reinsertion	38
Infection	52
Pain	72

Table 3: The common complications associated with PTBD tubes.

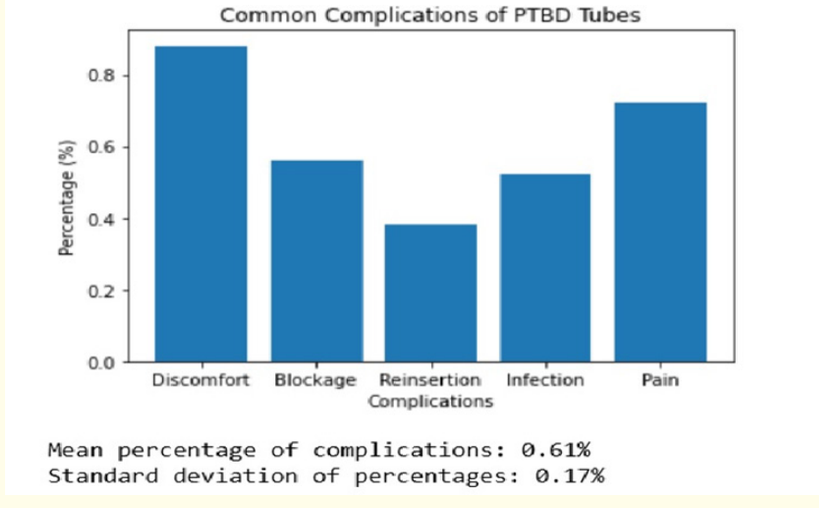

Figure 2

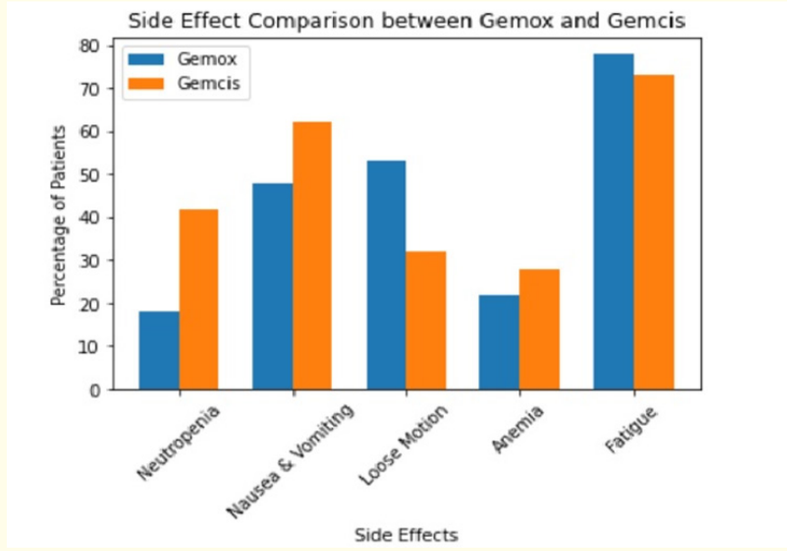

Figure 3

Discussion

According to Globocon 2018, gall bladder cancer is 22nd Cancer worldwide with 219,420 new cases which is 1.2% of malignancies and about 165,087 deaths contributing 17% of cancer related death. Incidence of gall bladder cancer varies according to geographic region. High rate of incidence reported in Central and South America, Eastern Europe and South-east Asia. India has second highest number of incidences of gall bladder cancer after China [26]. Within India disease varies with various geographical distribution. In India, it is more common in northern and eastern basin of Ganga and Brahmaputra [27]. Age standard rate of carcinoma gall bladder reported 11.8 per 100000 population in north and 17.1 per 100000 population in northeastern part of India [28]. The incidence of gall bladder cancer is rising in both sexes from 6.2 per 100000 population in 2001-2014 to 10.4 per 100000 population in 2012 to 2014 [29]. Gall bladder cancer is more common in females as compared to males 2-6 times worldwide. Study done by Gupta., *et al*. showed Female: Male ratio 2.9:1 [30].

Various etiological factor suggested ethnic predisposition on presence of environmental risk factor. In India, incidence of gall bladder cancer is 10 times higher in northern part of India compared to southern part [28]. Various other factors explain variation of incidence in different part across the country [31-40]. High risk region in India extends from Jammu and Kashmir, Punjab, Haryana, Himachal Pradesh, Uttarakhand, Uttar Pradesh, Bihar, Bengal, Assam, and Manipur. Majority part of these States based on major rivers are originating from glaciers and become polluted with industrial and human waste. Ganges supports a densely populated areas of human civilization especially lower section of society, they used to fulfil their daily needs. Untreated sewage material, Industrial and agricultural waste added into water along its course [38].

Bacterial Pathogens, *salmonella typhi* and *helicobacter pylori* have been established their association to cause gall bladder cancer are transmitted through faeco-oral route [33,36,41-43]. Cooking medium which is commonly used in north India is mustard oil. Carcinogenic adulteration like higher level of sanguinarine and diethyl nitrosamine found in blood and tissues of gall bladder cancer patients with cholelithiasis mustard oil has proinflammation properties and induce tumors [39].

Age and gender

In India mean age of presentation in gall bladder cancer reported younger than western world. Average age at diagnosis in India was reported 51+11 years while 71.2+12.5 years in western world [44-46]. Mean age in India with gall bladder cancer is usually 50-55 years.

In our Study, commonest age group was 45 to 55 years in males while 40-50 years in females. Women are 2-6 times higher risks to develop carcinoma gall bladder [47]. Patients having gall bladder stones are have higher risk to develop gall bladder [48]. Male, female ratio varies 1:3 to 1:4.5 in various Indian studies [49]. In our study, Male: Female ratio reported 1:1.8. Female hormone estrogen and Progesterone have the property to increase the salination of cholesterol in bile, resulting increased risk of gall stone

formation [14]. Indian women are commonly exposed to female hormone due to multiparity and early age of marriage. Due to lack of awareness and education females used to ignore initial symptoms related to gall bladder disease [50].

Gall stones

Gall Stones had the highest risk to develop gall bladder cancer with relative risk 4.9 [51]. About 85% of patients having gall bladder stone have history of cholelithiasis.

Various studies have shown relevance of gall bladder stones in 70-90% of patients with carcinoma gall bladder [9,40,41]. Gall stones are strongly associated with gall bladder cancer is not clear [52]. Common theory which describes its association with gall bladder cancer is exposure of carcinogens like secondary bile acid cause chronic irritation leads to develop metaplasia, dysplasia, and carcinoma [53].

A recent medical study shown gall stones were found to be 0.5% [26]. Relative risk of gall stones to change in gall bladder cancer ranges between 3 to 24 [54-58]. Size of gall stones; RR to develop gall bladder cancer increases with increase of size of gall bladder stones [59-61]. Duration of gall stones also associated with RR to develop gall bladder cancer increases with duration. RR was reported in 4.9 for duration of 5-19 years and 6.2 if duration is more than 20 years [62]. A large south Korean patient's study have shown gall stones were significantly associated with increase the incidence of gall bladder cancer and related mortality [63]. A study done by Khan., *et al*. shown Porcelain gall bladder was found only 2% to 3% [64]. Chronic infection of *S-typhi* and *helicobacter pylori* and *H. Billis* shown their association to cause gall bladder cancer [65-70]. Study done in Egypt shown patients have cholecystitis with *H. Pylori* infection shown metaplasia in 28%. *H. Billis* has been also shown association with gall bladder cancer [66,67].

Obesity with high body mass index have increased risk to develop gall bladder cancer [71-74]. A meta-analysis of 5902 cases shown BMI above 25 kg/m^2 have high risk of 4% with each increase of 1 kg/m^2 [75]. Toxic substance which are consumed excreted into bile and causes irritation of gall bladder mucosa. Worker of rubber plant, textile industries, nitrosamine compound shown an increased risk of Ca gall bladder [76]. Residents of Gangetic belt area, industrial area, were having high levels of pollutants in water have 10-fold increased risk to develop carcinoma gall bladder [76]. Begnadi., *et al*. shown heavy drinking > 50 Gm alcohol daily associated with gall bladder RR 2.64 [77]. Cigarette smoking has shown association with gall bladder cancer [78,79,82]. They observed jaundice in 59.5% and most common presentation was loss of appetite and weight loss 54.8%. Other studies shown pain in abdomen was commonest symptoms followed by jaundice 51.47% [82]. Study done by Kumar., *et al*. shown to 55% of patients have shown metastatic disease and 45% with locally advanced disease which is comparable to other studies of India. In our study, 75% Patients presented to locally advanced disease.

Lei and Lau [83] showed pain was most common presentation in 54-83%, Jaundice in 10-46% pain in 35.8%, Dubey., *et al*. shown pain was present in all patients. Gupta., *et al*. reported lump in abdomen in 3-6% and Lei and Lui reported in 3-8% [84]. In our study, Pain was commonest symptom with 83%. Jaundice was present in 48% cases. Obstructive jaundice was in 51% cases reported by Dubey., *et al*. 85.8% cases reported by Gupta., *et al*. In our study, Cholelithiasis was in 32% cases. Cholelithiasis was reported in 61.6% in Dubey., *et al*. 44% in Gupta., *et al*. Dubey., *et al*. reported in Stage III disease in 72% cases, 71.4% in Gupta., *et al*. study. In our study, liver metastasis was found in 22% in Dubey., *et al*. study, 23.3% in Gupta., *et al*. study. Malignant ascites were present in 72% in Dubey., *et al*. 23% in Gupta., *et al*. study. Regional lymph node and omental deposit found in 54% and 20% in Dubey., *et al*. study in Gupta., *et al*. reported it was 23% and 1%.

Value of CA 19.9 was very high in our study about 2000 to 175000 ml/dd. Clarke T., *et al*. also reported higher value of CA 19.9 in their study in meta static gall bladder cancer [85]. CA 19.9 tumor marker not specific for gall bladder, it should be combined with other investigation for diagnosis [86]. Level of CEA has been reported by Defernaic., *et al*. [87] was significantly higher in gall bladder cancer. Sensitivity and specificity were 0.66 and 0.90 Clarke T., *et al*. study sensitivity and specificity were 0.75 and 0.71 respectively in Defernaic., *et al*. for CA 19.9 and CEA [88]. In our Study, CEA was raised in 78% patients.

CA 19.9 is found to be elevated in digestive system tumors, pancreas, and biliary tract [89]. CA 19.9 is a diagnostic indication as well as a prediction for treatment response and prognosis of gall bladder cancer. Study done by Wong shown value of CEA was limited for diagnosis and prognosis of gall bladder cancer [90]. CA 19.9 has highest sensitivity but low specificity, it can be used in combination to show more efficacy for diagnosis of gall bladder.

LDH was raised in 38% and CA 125 was higher in 58% cases. Commonly and emerging drug regime is GEMOX as a single agent as or in combination. Dovel., *et al*. Shan 38% response rate and median survival was 20 weeks with Gemcitabine and cisplatin regimen [91]. Andre., *et al*. shown median PFS 8.5 month [92]. Singh., *et al*. shown median PFS 7.4 month with GEMOX regimen. In our study Gemcitabine (1000 mg/nm^2) and Oxaplatin (100 mg/nm^2) used in 160 patients, Gemcitabine (1000 mg/nm^2) and Cisplatin (40 mg/nm^2) D1 and D8 Regimen was used in 150 patients. About 63% patients were received 4 cycles of chemotherapy in GEMOX arm [93]. 60% Patients completed 4 cycles in GEMOX arm. 37% (190) Patients received palliative treatment in the form of supportive treatment, weekly chemotherapy and pain reliever. Survival rate of patient who undergone PTBD was only 4-6 months in 12% patients. Patients with PTBD developed infection at PTBD site, increase level of bilirubin, fever, weakness, anorexia, pain and infection at the site of PTBD.

Reinserting of PTBD tube required in 28% patients, in single line and 8% Patients required reinsertion of tube 2-4 times. Majority of our patients presented with Stage III and IV disease about 89% survival of stage IV patients was 4 to 8 months, while stage III patients survival was 10 months to 20 months. Gall bladder cancer is most common cancer in this region, in HBCR registry program with high mortality rate due to advancement of disease. Similar study done in Delhi also shown similar survival rate. In a retrospective study of 634 patients – 6 months for Stage IV disease and 25 months for Stage III disease. Similar results also shown by study by Behera., *et al*. with 1002 patients with 5.3-month median survival in Stage IV Patients and 26 months in stage III patients [94]. Common side effects in our study with Gemox regimen were loose motion, neutropenia in 53%. While side effects in Gemcis arm were neutropenia, Anemia in 42% (not statistically significant).

Patients required PTBD have shown less survival due to delayed treatment because of high bilirubin. Many times bilirubin level didn't decrease very fast, it takes 1 to 2 months to come down, it causes disease advancement.

Conclusion

Based on all available data in HBCR registry, Ca gall bladder cancer is the commonest cancer and showing increasing trend of Ca gall bladder cancer. Due to lack of awareness, poor hygiene, habit of spicy food intake, lack of exercise and fruit intake, use of unfiltered drinking water, unavailability of diagnostic facilities at rural area. Patients usually present with advance stage of disease which resulted high morality. Majority of patients subjected to Palliative treatment in the form of chemotherapy.

Planning to be done with more focus for screening and diagnostic technology in the form of Radiology and Pathology, so patients can be diagnosed early by screening and subjected to surgery followed by adjuvant treatment. Thus, we can reduce the mortality with Ca gall bladder.

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